A Dissertation on

ASYMPTOMATIC BACTERIURIA IN TYPE 2 DIABETIC WOMEN

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CERTIFICATE

This is to certify that this dissertation in **"ASYMPTOMATIC BACTERIURIA IN TYPE 2 DIABETIC WOMEN "** was a work done by **Dr.K.ESWARAN** under my guidance during the academic year 2004-2007. This has been submitted in partial fulfillment of the award of M.D.Degree in General Medicine (Branch-I) by the Tamil Nadu Dr.M.G.R. Medical University, Chennai - 600 032.

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DECLARATION

I solemnly declare that this dissertation entitled **"ASYMPTOMATIC BACTERIURIA IN TYPE 2 DIABETIC WOMEN"** was done by me at Madras Medical College and Government General Hospital during the academic year 2004 - 2007 under the guidance and supervision of **Prof.P.Thirumalaikolundusubramanian, M.D**. This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University, towards the partial fulfillment of requirement for the award of M.D. Degree in General Medicine (Branch - I).

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CONTENTS

INTRODUCTION

Diabetes is a Greek word - means "Siphon" ie., to pass through. Mellitus has the meaning of "honey", derived from Latin. Diabetes mellitus is a group of metabolic diseases characterised by hyperglycemia resulting from defects in insulin secretion, insulin action or both [1,2,3].

Type 2 diabetes mellitus which was previously known as noninsulin dependent or maturity onset diabetes, is the commonest form of the disease, accounting for 85-95% of all cases worldwide and affecting 5-7% of the world's population[4].

Diabetes produces various acute and chronic complications. Diabetic ketoacidosis, hyperosmolar nonketotic hyperglycemia, lactic acidosis are important acute meabolic complications. Chronic complications include microvascular (neuropathy, nephropathy and retinopathy) and macrovascular (cerebrovascular accident, cardiovascular disease and peripheral vascular disease).

Infection is a leading cause of hospitalisation among diabetic patients. Diabetes is associated with increased risk of developing infection[5,6], increased severity of infection and prolonged hospital stay[7,8]. Urinary tract infection, respiratory tract infection and soft tissue infection are common infections with increased incidence in diabetes. Altered host defenses, vascular abnormalities, frequent hospital admissions are responsible for increased incidence.

Urinary tract being the prevalent infection site[9,10], serious complications of urinary infection such as emphysematous cystitis, pyelonephritis, renal or perinephric abscess, bacteremia and renal papillary necrosis occur more commonly in diabetic patients[11].

Many urinary tract infections are asymptomatic and whether the symptomatic urinary tract infections are preceded by asymptomatic bacteriuria (ASB) is not known[12,13]. In contrast with men, development of ASB in diabetic women is much more common than in nondiabetic women[9,12,13,14,15]. Some investigators however, have been unable to confirm this findings[16,17].

Various risk factors for ASB in women with diabetes have been suggested including age, duration of diabetes, complications of diabetes [13,14,15,18,19,20,21], glucosuria and pyuria[22].

Due to the importance of UTI complications, observed to a greater extent in diabetic patients and because renal involvement even without the presence of symptoms (example - subclinical pyelonephritis) is common[23,24] investigating the association between ASB and symptomatic UTI in women with diabetes is important.

Therefore it was determined to study ASB in type 2 diabetic women, since no published reports on this area is available from this part of the country.

AIMS OF THE STUDY

- To find out the prevalence of Asymptomatic Bacteriuria in type 2 diabetic women.
- To analyse the spectrum of organisms responsible for Asymptomatic Bacteriuria in this group and its antimicribial sensitivity pattern.
- To correlate ASB with patient status (age, duration of diabetes, complications, etc).
- To design an algorythm so as to identify and treat ASB in type 2 diabetic women.

REVIEW OF LITERATURE

DIABETES MELLITUS

DEFINITION

Diabetes mellitus is a group of metabolic diseases charecterised by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action or both[1,2,3].

HISTORY OF DIABETES MELLITUS[24a]

Polyuric states resembling diabetes mellitus have been described for over 3500 years. It was described in an Egyptian papyrus dating from 1550 BC, discovered by Georg Ebers and a clearly recognisable description was given by Aretaeus of Cappadocia in the 2nd century AD. The term `diabetes' was first used by Aretaeus. The Hindu physicians, Charak and Sushrut, who wrote between 400 and 500 BC, were probably the first to recognise the sweetness of diabetic urine. The term `mellitus' was added by John Rollo in the late 18th century.

In 1776, Matthew Dobson concluded that diabetes was a systemic condition, not a disease of the kidneys. The excess sugar in diabetes was identified as glucose by Chevreul in 1815. The role of pancreas was

demonstrated in 1889 by Oskar Minkowski and Josef Von Mering. Pancreatic `islets' was described in 1869 by Paul Langerhans.

Insulin was discovered at the University of Toronto in 1921 by Frederick Banting, Charles Best, Macleod and James Collip. The name `insulin' was coined by Macleod. Leonard Thompson was the first patient to receive insulin.

EPIDEMIOLOGY

Prevalence of diabetes in adults worldwide was estimated to be 4.0% in 1995 and to rise to 5.4% by the year 2025[4]. It is higher in developed than in developing countries. The number of adults with diabetes in the world will rise from 135 million in 1995 to 300 million in the year 2025. The major part of this increase will occur in developing countries. There will be a 42% increase, from 51 to 71 million, in the developed countries and a 170% increase, from 84 to 228 million, in the developing countries. Thus, by the year 2025, >75% of people with diabetes will reside in developing countries, as compared with 62% in 1995.

The countries with the largest number of people with diabetes are, and will be in the year 2025, India, China and the U.S.

In India, estimated number of adults with diabetes was 19.4 million in 1995 and will be 57.2 million in 2025. According to WHO Ad Hoc Diabetes reporting group[4], prevalence of diabetes in India was estimated to be 3.8% in 1995, 4.0% in 2000 and will be 6.0% in 2025. Prevalence of diabetes in Indian study (PODIS)[25] showed that prevalence of type 2 diabetes was found in 7.06% and Imparied fasting glucose (IFG) in 7.87%.

Epidemilogical studies in India in the last decade have highlighted that not only is the prevalence of type 2 diabetes high, but that is increasing within the urban population. A recent survey showed that the prevalence of diabetes in urban adult was 12.1%. Prevalence of impaired glucose tolerance was also high 14.0%[26]. Prevalence of diabetes was found to be lower in low socioeconomic group living in urban areas compared with the high income group (12.6% Vs 24.6% in subjects $\geq$ 40 years).

Family history of diabetes, age, body mass index, waist:hip ratio, insulin resistance and sedentary life style showed positive association with diabetes in Indian populations.

CLASSIFICATION

The majority of cases of diabetes fall into two broad etiopathogenetic categories, now called type 1 and type 2 diabetes.

Because of the increasing number of forms of diabetes for which a specific etiology can be recognised. The current clinical classification proposed by the American Diabetes Association (ADA) in 1997[1] and adopted by the World Health Organisation (WHO) in 1999[27] classifies diabetes according to etiology.

This classification differs from previous classification, which used the terms insulin dependent diabetes (IDDM), and non-insulin dependent diabetes (NIDDM). The terms type 1 and type 2 diabetes (with Arabic numerals) have been adopted for the most common forms of diabetes mellitus.

Etiologic classification of diabetes mellitus

I. Type 1 diabetes

(β cell destruction, usually leading to absolute insulin deficiency).

A. Immune mediated

B. Idiopathic

II. Type 2 Diabetes

(May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance).

III. Other specific types

A. Genetic defects of β cell function

B. Genetic defects in insulin action

C. Diseases of the exocrine pancreas

d. Endocrinopathies

E. Drug or chemical induced

F. Infections

G. Uncommon forms of immune mediated diabetes

H. Other genetic syndromes sometimes associated with diabetes

IV. Gestational Diabetes Mellitus (GDM)

DIAGNOSTIC CRITERIA[1,2]

Three ways to diagnose diabetes are possible, and each, in the absence of unequivocal hyperglycemia, must be confirmed, on a subsequent day, by any one of the three methods.

1. Symptoms of diabetes plus casual plasma glucose concentration $\geq$ 200 mg/dl (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal.

The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

(or)

2. Fasting plasma glucose $\geq$ 126 mg/dl (7.0 mmol/L). Fasting is defined as no caloric intake for atleast 8 hours.

(or)

3. 2 hour post load glucose $\geq$ 200 mg/dl (11.1 mmol/L) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

TYPE 2 DIABETES MELLITUS

Type 2 diabetes is the most common form of diabetes. It accounts for 85-95% of those with diabetes. It is characterised by disorders of insulin action and insulin secretion, either of which may be predominant feature. Usually, both are present at the time when diabetes becomes clinically manifest. Although the specific etiology is not known, autoimmune destruction of the β-cells does not occur.

Patients with type 2 diabetes usually have insulin resistance and relative, rather than absolute, insulin deficiency. At the time of diagnosis

of diabetes, and often throughout their lifetime, these patients do not need insulin treatment to survive, although ultimately many require it for glycemic control. This form of diabetes is associated with progressive β-cell failure with increasing duration of diabetes. Ketoacidosis seldom occurs spontaneously but can arise with stress associated with another illness such as infection.

Most patients are obese and obesity aggravates the insulin resistance. Type 2 diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and in the earlier stages is not severe enough to produce the classic symptoms of diabetes. However such patients are at increased risk of developing macrovascular and microvasular complications. Their circulating insulin levels may be normal or elevated, yet insufficient to control blood glucose levels within the normal range because of their insulin resistance. Thus, they have relative rather than absolute, insulinopenia. Insulin resistance may improve with weight reduction or pharmacological treatment and results in normalisation of their glycemia.

Type 2 diabetes is seen frequently in women who have a previous history of gestational diabetes and in individuals with other characteristics of the insulin resistance syndrome, such as hypertension or dyslipidemia.

The risk of developing type 2 diabetes increases with age, obesity and physcial inactivity. Type 2 diabetes shows strong familial aggregation, so that persons with a parent or siblings with the disease are at increased risk.

ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria is frequently detected in routine investigations. This is defined[28] as > 10^5 cfu/ml organisms in the urine of apparently healthy asymptomatic patients. Approximately 1% of children under the age of 1, 1% of schoolgirls, 0.03% of school boys and men, 3% of non-pregnant adult women and 5% of pregnant women have asymptomatic bacteriuria. In females, asymptomatic bacteriuria increases upto 10% until an age of 65 years[29].

There is no evidence that this condition causes renal scarring in adults who are not pregnant and have a normal urinary tract. Upto 30% of patients will develop symptomatic infection within one year. The dilatation of the urinary tract during pregnancy allows bacteria to ascend easily to the kidneys.

Treatment of asymptomatic bacteriuria remains controversial. It has been proposed that transient bacteriuria merely reflects colonisation of the bladder without tissue invasion, which clears spontaneously and returns, or probably turns into true infection with pyuria over the time.

In general there is little evidence that routine treatment of positive cultures are required, except during pregnancy, children, patients for kidney transplantation and elderly bedridden patients.

PREVALENCE OF ASB IN DIABETES MELLITUS

Whether UTI and asymptomatic bacteriuria are more prevalent in diabetic women than in nondiabetic women has been debated for decades. More controlled studies have examined the prevalence of bacteriuria in diabetic compared with nondiabetic subjects than any other infection.

Kass[30] in 1957 and several other investigators[12,31-38] estimate that the prevalence of ASB is about 3 times higher in diabetic women (ranging from 15% to 25%) than in nodiabetic women (less than 10%).

One study[15] that sampled diabetic (including those previously undiagnosed) and control nondiabetic subjects from a defined community found a higher bacteriuria prevalence associated with diabetes. These data therefore support a higher prevalence of bacteriuria in diabetic subjects. In some studies, however the reported prevalence of asymptomatic bacteriuria in diabetic women has been 10% or less[14,38-40].

PATHOGENESIS OF ASB IN DM

1. Altered host defenses in diabetes

(a) Innate cellular immunity

Several different immune deficits have been described in diabetics. Cell mediated immunity seems to be most affected, with abnormalities of

polymorphonuclear leucocytes (PMNLs), monocytes and lymphocytes reported. Numerous researchers have studied PMNLs in the past, reporting abnormalities of adherence[41,42], chemotaxis[43,44], phagocytosis[45], oxidative burst[46-49] and microbicidal ability[48,50,51]. All can improve with tighter glycemic control.

The intracellular killing of organisms by leucocytes is mediated by releasing of toxic free radicals, superoxides and hydrogen peroxide. This `respiratory burst' is defective in diabetes mellius. Diliamaire[52] found significantly lower chemotaxis among both type 1 and type 2 diabetics and although there was an increased expression of certain adhesion molecules and evidence of spontaneous activation of PMNLs with increased free radical activation, the neutrophil response after stimulation was lower than in controls.

Gallacher et al[53] found a significantly negative correlation between glycated hemoglobin levels and neutrophil bactericidal activity. The presence of advanced glycation end products leads to a state of low level persistant activation in PMNLs, as evidenced by increased concentration of neutrophil elastase, increased activity of neutrophil alkaline phosphatase and luminol dependent chemiluminescence and an increased rate of neutrophil oxygen consumption among unstimulated PMNLs of diabetic patients[54,55]. This hyperexited state leads to spontaneous activation of the oxidative burst and release of myeloperoxidase, elastase, and other neutrophil granule components that can be detrimental in two ways.

1. May lead to a `burned out or tolerant' PMNLs that responds less vigorously when stimulated by an infectious pathogen and

2. May initiate pathologic process leading to vascular injury, thus producing vascular complications.

Hyperglycemia and acidemia may both affect PMNL, function[56], chemiluminescence studies have revealed improvement in phagocytic function with improved glycemic control[45]. Abnormalities in monocyte / macrophage chemotaxis and phagocytosis also have been reported.

(b) Adaptive Cellular and Humoral Immunity

Adaptive humoral immunity in diabetics appears to be normal with normal levels of immunoglobulins and normal response to vaccination. Adaptive cellular immunity does appear to be affected[57].

(c) Complement

Hyperglycemia may result in defective complement mediated functions - for example, the defect in the opsonic binding site of the C3 component of complement, increases susceptibility to candida infection[58].

2. Increased adherence of uropathogens to bladder epithelial cells

Researchers have sought to determine whether the increased adherence of bacteria to uroepithelial cells in diabetic women is to blame

for the increased prevalence of UTIs and asymptomatic bacteriuria in this population. Recent studies[59,60] shows that uropathogenic E.coli expressing type-1 fimbriae were twice as adherent to cells from women with diabetes as compared with cells collected from the women without diabetes. Uroepithelial cells from women with diabetes may have intrinsic differences in nature and/or amount and/or affinity of binding receptors for type -1 fimbriae. (Type-1 fimbriae - the virulence factor that plays an important role in the pathogenesis of UTIs.)

3. "Sweet urine" Theory : The effects of glucosuria on the growth of uropathogens in diabetic persons

High level of glucose in the urine of persons with diabetes might cause uropathogens to flourish. Geerlings and associates[61] found that moderate and severe glucosuria (glucose concentration between 100 and 1000 mg/dl) enhanced bacterial growth in vivo. Bacterial growth in vitro was increased after the addition of different glucose concentration[60]. Murphy DP et al[62] and Mohammed Ali Bouroumand et al[22] observed a significant relationship between bacteriuria and glucosuria. These studies conclude that glucosuria may be one factor contributing to the increased prevalence of bacteriuria in diabetic persons.

4. Others

Endothelial dysfunction, oxidative stress and the increased formation of advanced glycation end products may play a role in the development of diabetic complications and also contribute to the development of infections[63,64,65]. Incomplete bladder emptying due to autonomic neuropathy permits urinary colonisation by microorganisms[66,67].

PATHOGENS IN DM

For the most part, the same organisms cause UTI in diabetic patients as in nondiabetic patients. Escherichia coli in diabetic patients as in others, is the most common uropathogen. Other Enterobacteriacea (including Proteus, Klebsiella, Enterobacter and Citrobacter species), Pseudomonas aeruginosa, Enterococcus species, Streptococci, Staphylococci, Candida albicans and other fungi have been reported.

The percentage of infection with E.coli is lower in diabetic persons than non-diabetics[31,68] and the percentage of infection with Klebsiella species is higher in diabetic persons than in those without diabetes[68]. In a few study microorganism was different. For example Klebsiella was the most common organism in the Alebiosu study[69].

Fungal UTIs caused by candida or Torulopsis slabrata are also more common in persons with diabetes than in those without[9].

COMPLICATIONS

Frequency of symptomatic urinary tract infections is higher among women with diabetes than among those without diabetes[18,70]. Furthermore, localisation studies have shown that infection of the upper urinary tract at initial testing is more common among women with bacteriuria and diabetes (occuring in 63 percent) than among women with bacteriuria but no diabetes (43 percent). Eighty percent of women with diabetes and bacteriuria have been shown to have renal parenchymal infection by seven weeks after initial testing[23,36].

An autopsy series documented a frequency of acute pyelonephritis among patients with diabetes that was four to five times as high as that among patients without diabetes[71]. The urinary tract is also a more common source of bacteremia among patients with diabetes[5,70].

Finally among women with diabetes, complicated symptomatic urinary tract infections are associated with higher frequencies of acute pyelonephritis, urosepsis and bilateral renal infection and a higher risk of hospitalisation than they are among nondiabetic women with symptomatic bacteriuria[70,72].

Other serious, although less common, complications of bacteriuria associated with diabetes include renal and perirenal abscesses, emphysematous cystitis, emphysematus pyelonephritis, renal papillary necrosis, fungal urinary tract infections and xanthogranulomatous pyelonephritis.

MANAGEMENT OF ASB

Diabetes mellitus with symptomatic bacteriuria is serious and warrants proper clinical attention for both diagnosis and treatment. Because of the frequent upper urinary tract infections and complications, most investigators recommend cultures for all urinary tract infections in patients with diabetes. Follow up urine culture after completion of antimicrobial therapy is also recommended for most women with diabetes in order to identify patients in whom bacteriologic cure has not been achieved[70].

Many investigators[70] have recommended screening patients with diabetes to detect and then treat asymptomatic bacteriuria because of the increased frequency and severity of upper urinary tract infections associated with symptomatic bateriuria in such patients, even though there are few data to support this recommendation.

Results from a study of women with diabetes who were treated for asymptomatic bacteriuria demonstrated no reduction in complications[73]. Although there were short term results in clearing bacteriuria with antimicrobial therapy, there was no decrease in the number of symptomatic episodes or hospitalisation over the long term. Furthermore, the high rate of recurrence of bacteriuria in those who were screened and treated, resulted in a marked increase in the use of antimicrobial agents.

Endre Ludwig et al[74] recommend atleast one course of appropriate antibiotic therapy in an effort to eradicate the pathogen or the postulated pathogen from the urinary tract, but this is based solely on empiric evidence.

Harding et al have been conducting a prospective study and preliminary data suggest a higher frequency of pyelonephritis and hospitalisation in women with untreated asymptomatic bacteriuria. These investigators stress, the importance of prophylactic antibiotic therapy.

Fluroquinolones, betalactamase stable penicillins or cephalosporins are recommended antimicrobials for empiric therapy for ASB in diabetic patients. Recommended duration of treatment is 7 -10 days.

MATERIALS AND METHODS

Setting

Outpatient sections of the Department of Diabetology and the Institute of Internal Medicine, Madras Medical College and Government General Hospital, Chennai - 3.

Collaborating Departments

The Department of Diabetology and the Institute of Microbiology, Madras Medical College and Government General Hospital, Chennai-3.

Study design

Single centre, cross sectional and analytical study.

Period of study

The work was carried out from January 2006 to August 2006, continuously over a period of eight months.

Inclusion criteria

Adult women with type 2 diabetes mellitus who gave voluntary consent were included.

Exclusion criteria

Those who had one or combination of the following were excluded.

- Symptoms of UTI - including dysuria, frequency, urgency, abdominal discomfort, fever etc.
- Vulvovaginitis
- Pregnancy
- Recent hospitalisation or surgery (<4 months)
- Known urinary tract abnormalities (including cystopathy, etc.)
- Recent urinary tract instrumentation (catheterisation, etc.)
- Culture positive for three or more organisms, funguria
- Use of antimicrobials in the last 14 days
- Past history of UTI
- Hypertension

Sample size

Study subjects: 238 type 2 diabetic women

Control subjects: 64 nondiabetic women

Consent

An informed consent was obtained from participants.

Selection of study and control subjects

Study subjects

Women with type 2 diabetes were recruited randomly from the outpatient section of the Institute of Internal Medicine and diabetes outpatient clinics of the Diabetology Department, Madras Medical College and Government General Hospital. All are married and having children. They were treated with oral hypoglycemic agents or insulin or both. All were normotensives. Initially 238 patients were selected, among them 74 were excluded (symptoms of UTI-11, vulvovaginitis-3, use of antimicrobials-2, past history of UTI-28, culture positive for Candida albicans-4, culture positive for three or more organisms-5 and hypertension - 21).

Control subjects

Women without diabetes were selected randomly from the general population. They were relatives and friends of inpatients admitted in general medical ward. Exclusion crieteria were the same as for diabetic women. Among them eight were excluded (positive UTI symptoms-4, hypertension - 2, use of antimicrobials-1 and culture positive for three or more organisms-1).

Details of study subjects

Their ages ranged from 31 to 80 years. All study subjects were interviewed during the first visit of the study and their medical history was obtained. This information included age, duration of diabetes, medications, complications of diabetes. The following laboratory data were included: fasting plasma glucose, blood urea, serum creatinine, albuminuria, glucosuria and leucocyturia. These patients were evaluated for microvascular and macrovascular complications of diabetes. Due to technical constraints practical concerns HbA_{1C} could not be done. Due to social concerns sexual history could not be obtained.

Details of control subjects

Their ages ranged from 32 to 76 years. All were interviewed and their non diabetic status was confirmed by using 2 hour oral glucose tolerance test[1,2]. Agewise distribution of control subjects were similar to study subjects. Laboratory data included were fasting plasma glucose, blood urea, serum creatinine, albuminuria, glucosuria and leucocyturia.

Definitions

Diabetes mellitus

According to the American Diabetes Association Criteria[1,2], a fasting plasma glucose concentration of ≥7.0 mmol/L, a 2 hour

(post glucose) plasma glucose concentration of ≥ 11.1 mmol/L or the use of glucose lowering medications (oral agents or insulin).

Asymptomatic bacteriuria

Asymptomatic bacteriuria is defined as the presence of atleast 10^5 colony forming units/ml of 1 or 2 bacterial species in clear voided midstream urine sample from an individual without symptoms of urinary tract infection[28].

Presence of atleast 3 microorganisms in one urine specimen was considered as contaminated urine and these specimens were excluded. Cultures positive for Candida species were not considered as positive because this study was confined to bacteriuria.

Glucosuria and proteinuria

Glucosuria and proteinuria were defined as any level of glucose or protein, respectively, above a trace level on urine analysis.

Leucocyturia (Pyuria)

Leucocyturia is defined as more than five leucocytes per high power field.

Urinary samples

Each individual was explained on the technique of urine collection. Midstream clean voiding urine specimens were collected in a wide mouthed sterile container for the evaluation of bacteriuria. All urine samples were immediately sent to Microbiology laboratory and were cultured. Urine culture was performed according to standard procedure. All urine samples were cultured on Cystein Lactose Electrolyte Deficient (CLED) agar. Antibiotic sensitivity was tested by using Muller-Hinton agar plate by Kirby Baur's disc diffusion method. Ciprofloxacin, Ofloxacin, Amikacin, Gentamicin, Penicillin-G, Cefotaxime and Cefaperazone sulbactum were the drugs used, as they were used in this hospital at the time of study. Instead of Penicillin-G, Oxacillin was used for Enterococci.

Glucosuria and proteinuria were assessed by using Benedict's method and Turbudimetric method respectively.

Conflict of interest

There was no conflict of interest.

Financial support

This work was not supported by any funding agency or charitable organisation.

Statistical analysis

Differences between patients with and without ASB were obtained through

`t test' for continuous variables (age, duration of diabetes, urea, creatinine). For nominal variables `Chi-Squared test' was used. In addition, by using leucocyte as a dependent variable and age, duration of diabetes, nephropathy, neuropathy, ischemic heart disease as independent variables, multiple logistical regression analysis was used. Data were analysed by SPSS statistical software and P value of <0.05 was considered significant. Mean values are reported as mean ± standard deviation.

RESULTS

There was 164 participants in the study group and 56 nondiabetic women in the control group. Their characteristics are provided below in Table 1 and Table 2 respectively.

Table 1: Characteristics of study group

Characteristics	Median	Mean ± SD
Age (years)	52.0	52.4 ± 11.2
Duration of diabetes (years)	5.0	6.3 ± 4.5
Plasma glucose (mmol/L)	7.2	7.9 ± 3.1
Blood urea (mmol/L)	3.6	3.7 ± 0.8
Serum creatinine (μmo1/L)	88.0	87.2 ± 29.0

Table 2: Characteristics of control group

Characteristics	Median	Mean ± SD
Age (years)	50.0	51.1 ± 11.8
Plasma glucose (mmol/L)	4.6	4.6 ± 0.6
Blood urea (mmol/L)	3.5	3.5 ± 0.2
Serum creatinine (μmo1/L)	71.0	74.3 ± 10.5

Study group ages ranged from 31 to 80 years with a mean of 52.4 ± 11.2 and median of 52 years. Duration of diabetes in this group was between 1 to 20 years with a mean of 6.3 ± 4.5 and median of 5 years. Mean values of plasma glucose, blood urea and serum creatinine were 7.9 ± 3.1, 3.7 ± 0.8 mmol/L and 87.2 ± 29.0 μmol/L respectively.

Control group ages ranged from 32 to 76 years with a mean of 51.1 ± 11.8 and median of 50 years. Mean values of plasma glucose, blood urea and serum creatinine were 4.6 ± 0.6, 3.5 ± 0.2 mmol/L and 74.3 ± 10.5 μmol/L respectively.

Age wise distribution of the individuals belonging to study group and control group is given in Table 3 and Table 4 respectively. Majority of study subjects belonged to age group 51 to 60 which was followed by 41 to 50 years.

Table 3: Study group-Age wise distribution

Age (years)	Number (164)	Percentage
30-40	30	18.3
41-50	46	28.0
51-60	53	32.3
>60	35	21.3

Table 4: Control group-Age wise distribution

Age (years)	Number (56)	Percentage
30-40	12	21.4
41-50	17	30.4
51-60	16	28.6
>60	11	19.6

Majority of control subjects were belonged to age group 41 to 50 which was followed by 51 to 60 years.

Based on the duration of diabetes, study group was further subdivided into 3 groups as shown in Table 5. Most of them (79.8%) were less than 10 years of duration.

Table 5: Study group-duration of diabetes

Duration of diabetes (years)	Number (164)	Percentage
<5	74	45.1
5-10	57	34.7
>10	33	20.1

Micro and macrovascular complications of the study group are provided in Table 6 given below. Among them, neuropathy, retinopathy and cardiovascular complications were observed in 24.3, 19.5 and 9.1% respectively.

Table 6: Study group-Micro and Macrovascular complications

Complications	Number (164)	Percentage
Microvascular		
Retinopathy	32	19.5
Nephropathy	11	6.7
Neuropathy	40	24.3
Macrovascular		
Cardiovascular system (CVS)	15	9.1
Central nervous system (CNS)	3	1.8
Peripheral vascular disease (PVD)	5	3.0

Among the study subjects proteinuria, glucosuria and leucocyturia were observed in 18.3, 24.4 and 20.1% respectively and the details as depicted in Table 7.

Table 7: Urine analysis - study subjects

Urine analysis	Number (164)	Percentage
Proteinuria	30	18.3
Glucosuria	41	24.4
Leucocyturia	33	20.1

Urine culture was positive in 37 participants in the study group and three participants in the control group which are provided in Table 8, eventhough they were asymptomatic.

Table 8: Prevalence of asymptomatic bacteriuria (ASB)

Subjects	Number (ASB positive subjects)	Percentage
Study group (n=164)	37*	22.56
Control group (n=56)	3	5.36

ASB - Asymptomatic bacteriuria *Significant ($p<0.001$)

Overall the prevalence of ASB was 22.56% in study group and 5.36% in control group. Analysis of the prevalence of ASB among study group and control group by Chi-Square test revealed that, ASB was significantly more among diabetes than control.

Characteristics of study subjects those with asymptomatic bacteriuria are shown in table 9, provided below.

Table 9: Characteristics of ASB positive study subjects

ASB positive study subjects (n=37)	Number	Percentage
Age group (years)		
30-40	6	16.2
41-50	11	29.7
51-60	16	43.2
>60	4	10.8
Duration of diabetes (years)		
<5	17	45.9
5-10	12	32.4
>10	8	21.6
Complications of diabetes		
Retinopathy	9	24.3
Nephropathy	8	21.6
Neuropathy	6	16.2
CVS	4	10.8
CNS	1	2.7
PVD	Nil	-
Urine analysis		
Glucosuria	19	51.3
Proteinuria	26	70.0
Leucocyturia	24	64.8

Among patients with bacteriuria (n=37), six (16.2%) were under 41 years old. Of study subjects between 41 to 50, 51 to 60 and more than 60 years 23.6, 30.1 and 11.4% had bacteriuria respectively.

Among patients with less than 5 years of diabetes 22.9% and patients with 5 to 10 years of diabetic history 21.0% had bacteriuria. Among the 33 patients who had diabetes of more than 10 years duration, 24.2% had bacteriuria.

Of the 37 patients who had positive urine culture, 70% had proteinuria. Among 41 study subjects with proteinuria, 63.4% had bacteriuria as well.

In this study, 64.8% of patients with bacteriuria also displayed leucocyturia and 92.9% of participants without bacteriuria showed no evidence of leucocyturia. Among patients with bacteriuria, 51.3% had glucosuria and patients without bacteriuria, 91.3% had no glucosuria. Among the glucosuria and leucocyturia positive study subjects, 63.3 and 72.7% had bacteriuria respectively.

Among the ASB positive study subjects, retinopathy, nephropathy, neuropathy, cardiovascular complications and cerebrovascular disease were observed in 24.3, 21.6, 16.2, 10.8 and 2.7% respectively. None of them had peripheral vascular disease.

The isolates (microorganisms) from urine cultures of both diabetic and nondiabetic women during the study period is provided in Table 10 given below.

Table 10: Microorganisms isolated

Microorganisms	Number	Percentage
Study subjects (n=37)		
Escherichia coli	17	45.9
Klebsiella	10	27.0
Coagulase negative staphylococci	4	10.8
Staphylococcus aureus	5	13.5
Enterococci	1	2.7
Control subjects (n=3)		
Escherichia coli	2	66.6
Klebsiella	1	33.3

The nature of the microbial isolates and its sensitivity as well as resistant pattern is shown in table 11.

Table 11: Microorganisms and its sensitivity pattern

Organisms	Ciprofloxacin	Ofloxacin	Amikacin	Gentamicin	Penicillin-G	Cefotaxime	Cefoperazone sulbactum
E.coli (n=17)							
Sensitive	7	7	17	13	NT	10	17
Resistant	10	10	0	4	NT	7	0
Klebsiella (n=10)							
Sensitive	7	7	10	7	NT	6	10
Resistant	3	3	0	3	NT	4	0
Coagulase negative staphylococci (n=4)							
Sensitive	1	4	4	NT	2	2	4
Resistant	3	0	0	NT	2	2	0
Staphylococcus aureus (n=5)							
Sensitive	1	2	5	NT	0	2	4
Resistant	4	3	0	NT	5	3	1
Enterococci (n=1)							
Sensitive	1	1	1	NT	0	0	1
Resistant	0	0	0	NT	1*	1	0

NT-Not tested * Oxacillin used

The association of asymptomatic bacteriuria was statistically analysed with age, duration of diabetes, micro and macrovascular complications of diabetes, blood biochemistry, glucosuria, proteinuria and leucocyturia. The association of leucocyturia with nephropathy, neuropathy and cardiovascular complications were also statistically analysed. Among them proteinuria, glucosuria, leucocyturia, nephropathy, plasma glucose and serum creatinine, had significant association with asymptomatic bacteriuria, but patients age, duration of diabetes, retinopathy, neuropathy and macrovascular complications were not. Their P values are given in Table 13 (next page).

Sensitivity, specificity, positive predictive value and negative predictive value of leucocyturia with reference to asymptomatic bacteriuria was 64.8, 92.9, 72.7 and 90.0% respectively shown in Table 12.

Table - 12

	ASB present	**ASB absent**	**Total**
Leucocyturia present	24	9	33
Leucocyturia absent	13	118	131
Total	37	127	164

Table 13: Asymptomatic bacteriuria in relation to characteristics

Variables	P value
ASB and age	0.22060^{NS}
ASB and duration of diabetes	0.93481^{NS}
ASB and retinopathy	0.40128^{NS}
ASB and nephropathy	<0.001**
ASB and neuropathy	0.37849^{NS}
ASB and CVS complications	0.68981^{NS}
ASB and CNS complications	0.65233^{NS}
ASB and PVD	0.22029^{NS}
ASB and plasma glucose	0.00439**
ASB and serum creatinine	0.00074**
ASB and proteinuria	<0.001**
ASB and glucosuria	<0.001**
ASB and leucocyturia	<0.001**
Leucocyturia and nephropathy	<0.001**
Leucocyturia and neuropathy	0.93999^{NS}
Leucocyturia and CVS complications	0.88113^{NS}

** Significant at 1% level NS-Not significant

ASB-Asymptomatic bacteriuria CVS-Cardiovascular system

CNS-Central nervous system PVD-Peripheral vascular disease

Multiple logistical analysis was also applied. In this analysis leucocyte was used as a dependent variable. It was analysed with independent variables such as age, duration of diabetes, nephropathy, neuropathy and cardiovascular complications. Asymptomatic bacteriuria was statistically noticed more among those with nephropathy.

DISCUSSION

Asymptomatic bacteriuria in diabetes mellitus should be considered and looked for while diabetic patients come for review. In this study 37 out of 164 type 2 diabetic women had asymptomatic bacteriuria and the prevalence of ASB was 22.56%. This is comparable with earlier studies by Alebiosu et al.[10] which was 26.6%; Joffe et al.[35], Kass et al.[32] and Hansen et al.[33] noticed ASB in 20, 18 and 18.5% respectively. Similaly Vejlsgaard et al.[12], and O'sullivan et al.[38] observed 18.8% and 19.8% of bacteriuria respectively. But more prevalence of ASB in diabetic women was reported in Geerlings et al.[31] study [both type 1 and type 2 diabetic patients -26% (163 of 636); type 2 diabetic patients - 29% (110 of 378)]. Jaspan et al.[37] reported 27% bacteriuria in diabetic patients.

Bahl et al.[34], 11.3%; Ooi BS et al.[36], 15.8%; and Mohammed Ali Boromand et al.[22], 10.6% studies showed increase in prevalence of ASB in diabetic women. Zhanel et al.[18], 7.9% (85 of 1072); Sawers et al.[20], 9.5% (38 of 400); and Schmitt et al.[14], 9.1% reported high prevalence of bacteriuria in diabetic women.

All these studies were shown 2 to 4 fold increase in prevalence of ASB in diabetic women than nondiabetic women. Some of the publications did not notice any difference in prevalence of bacteriuria between diabetic and nondiabetic men. Table 14 shows the various studies and prevalence of bacteriuria in diabetic population. These studies have been recently summarised and published[75].

TABLE - 14

STUDIES ON THE ASSOCIATION BETWEEN DIABETES AND BACTERIURIA

Outcome definition	Subjects (n)		Prevalence (%)		Adjustment factors	Author
	Diabetic	Nondiabetic	Diabetic	Nondiabetic		
Asymptomatic bacteriuria	F= 54 M =37	F=337 M=102	F=18.0 M=5.0	F=6.0 M=4.0	None	Kass EH[32]
Asymptomatic bacteriuria	F= 81 M =67	F= 81 M =67	F= 18.5 M =7.5	F= 7.5 M =3.0	Age and sex matched	Hansen RO[33]
Asymptomatic bacteriuria	F=97 M-149	n=100 Sex not specified	F=11.3 M=10.7	M& F = 3.0	None	Bahl et al.[34]
Asymptomatic bacteriuria	F=60	F=36	F=20	F=2.8	None	Joffe et al.[35]
Asymptomatic bacteriuria	F=152 M=154	F=152 M=159	F=15.8 M=1.3	F=4.6 M=0.7	Matched on age sex and parity	Ooi BS et al.[36]
Asymptomatic bacteriuria	Both type1 and type 2 diabetes F=636 Type 2 diabetes F=378	F=153	Both type 1 and type 2 diabetes F=26 Type 2 diabetes F=29	F=6	None	Geerlings et al.[31]
Asymptomatic bacteriuria	F=202	-	F=10.6	-	-	Mohammed et al.[22]

(Continued next page)

TABLE - 14 (Continued)

STUDIES ON THE ASSOCIATION BETWEEN DIABETES AND BACTERIURIA

Outcome definition	Subjects (n)		Prevalence (%)		Adjustment factors	Author
	Diabetic	Nondiabetic	Diabetic	Nondiabetic		
Bacteriuria	F=128 M=141	F=114 M=146	F=18.8 M=0.7	F=7.9 M=2.1	Similar age to sex distribution	Vejlsgaard R[12]
Bacteriuria	F=111 M=87	F=79 M=68	F=27.0 M=8.0	F=11.4 M=2.9	None	Jaspan et al.[37]
Bacteriuria	F=341 M=411	F=100 M=100	F=9.1 M=1.0	F=5.0 M=0	None	Schmitt et al.[14]
Bacteriuria	F=91 M=59	F=91 M=59	F=19.8 M=3.3	F=18.7 M=1.7	Similar age and sex distribution	O' Sullivan et al.[38]
Chemstrip LN	n=206 sex not specified	n=41 sex not specified	M&F = 5.8	M&F=1.7	Age, ethnicity, sex, country of residence	Keane et al.[15]
Asymptomatic bacteriuria	F=47 M=53	F=48 M=52	F=10.6 M=3.8	F=8.3 M=1.9	Age and sex matched	Vigg et al.[39]
Asymptomatic bacteriuria	F=100 M=90	F=100 M=90	F=9.0 M=3.3	F=8.0 M=2.5	Matched on age by decade and sex	Abu-Bakare et al.[40]
Asymptomatic bacteriuria	F=164	F=56	F=22.5	F=5.3	Age matched	Present study

M = Male F = Female n = number Source = Boyko et al.[75]

Like most other earlier studies, here also Escherichia coli was the most prevalent microorganism (45.9%) isolated from urine culture. In control group three subjects had positive urine culture, out of which two were E.coli. Lye et al.[68], observed that E.coli was the predominant microorganism in UTIs in diabetic patients, but E.coli occurs in significantly lower numbers than in control subjects, similar to the present study.

In a few studies the microorganisms were different. For example Klebsiella was the most common organism in the Alebiosu study[69]. In this study, Klebsiella is the second common organism (27%). Coagulase negative staphylococci (10.8%), Staphylococcus aureus (13.5%) and Enterococci (2.7%) are the other organisms isolated in this study group.

As in Table 11 (Page 36), most of the E.coli strains were sensitive to Amikacin, Gentamicin and Cefoperazone sulbactum. About half of them were resistant to Ciprofloxacin, Ofloxacin and Cefotaxime.

All Klebsiella strains were sensitive to Amikacin and Cefoperazone sulbactum. Approximately 30% of them resistant to Ciprofloxacin, Ofloxacin, Gentamicin and Cefotoxime.

Most of the Coagulase negative staphylococci were resistant to Ciprofloxacin and approximately 50% were resistant to Penicillin-G and

Cefotaxime. All of them were sensitive to Ofloxacin, Amikacin and Cefoperazone sulbactum.

Amikacin and Cefoperazone sulbactum were highly sensitive drugs for Staphylococcus aureus. Most of them were resistant to Ciprofloxacin, Ofloxacin and Cefotaxime.

Enterococci was sensitive to Ciprofloxacin, Ofloxacin, Amikacin and Cefoperazone sulbactum. This organism was resistant to Penicillin-G and Cefotaxime.

Sensitivity to the drugs like Ciprofloxacin, Ofloxacin, Gentamicin and Cefotaxime was declining. Frequent usage may be the attributable reason. However, most of the organisms were sensitive to Amikacin and Cefoperazone sulbactum. Further studies in this regard must be accomplished and the results should be compared with the antibiograms of nondiabetic patients.

Statistical analysis revealed a highly significant relationship between bacteriuria and leucocyturia ($p<0.001$). Mohammed Ali Boroumand et al.[22] reported that pyuria (leucocyturia) and glucosuria had a significant relationship with bacteriuria. Geerlings et al.[31, 76] found that macroalbuminuria was a risk for developing ASB. Macroalbuminuria as an expression of severe structural damage in the kidney, may increase the vulnerability to bacterial attacks, thus resulting in an increased risk of

developing ASB. In the present study significant ($p<0.001$) association between bacteriuria and proteinuria, bacteriuria and glucosuria were also noticed.

In this study, bacteriuria had a significant association with nephropathy ($p<0.001$) and elevated serum creatinine ($p<0.001$). Altered host defence mechanism in diabetes may be aggravated by development of nephropathy in diabetic patients and inturn it increases the prevalence of ASB. Some studies[14,18] showed that the presence of long standing complications (peripheral neuropathy, peripheral vascular disease) increased the risk of developing ASB. But here, except nephropathy, no other diabetic complications had significant association with ASB.

Some studies had shown[31,76] that glycemic control had no association with ASB. But here, ASB had significant association with fasting plasma glucose levels, but this may be unreliable because, plasma glucose levels highly variable with drugs (oral hypoglycemic agents or insulin), dietary intake and physical activity.

Eventhough age is a well known risk factor for bacteriuria in women without diabetes[77] and some studies have shown age as the most important risk factor for ASB in type 2 diabetic patients[31]. However, age had no significant relation with ASB in this study ($p=0.2206$). Most of the

earlier studies did not show any increase in the incidence of ASB in elderly population with diabetes[12, 14, 18, 19].

Some studies have shown that a longer duration of diabetes increases the risk of developing ASB[14, 18], while others could not confirm this notion[13, 16, 19]. In this study, duration of the disease was independent of ASB (p=0.9348).

Overall risk factors for ASB in type 2 diabetic women observed in the present study are provided in Table 15 below.

Table 15: Risk factors for women with type 2 diabetes

Risk factors	P value
Proteinuria	<0.001
Leucocyturia	<0.001
Glucosuria	<0.001
Nephropathy	<0.001
Plasma glucose	0.0044

Considering these risk factors, blood glucose is a highly variable factor, which depends on dietary intake, physical activity and regularity of treatment. Renal threshold to glucose is variable in different individuals and also in the same individual at different times. Hence glucosuria can not be considered as a sole criteria. Diabetic nephropathy

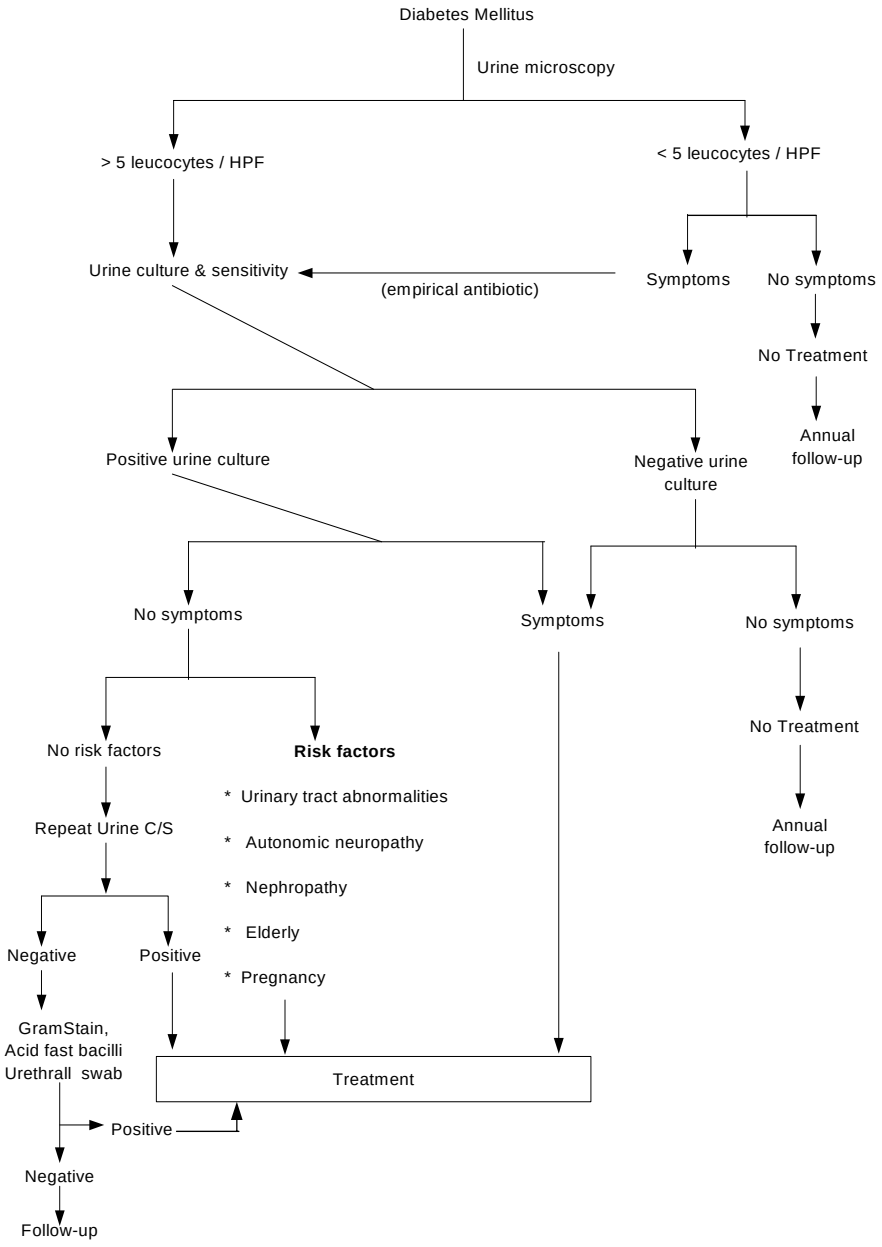
per se manifest as a proteinuric state and serum creatinine does not rise until more than 50% of GFR has been lost. At primary health care level early diagnosis and confirmation of nephropathy is not feasible till proteinuria becomes overt. Eventhough glucosuria, proteinuria and nephropathy were significantly associated with asymptomatic bacteriuria, at primary care level the applicability is variable.

To test urine culture and sensitivity, adequate lab facilities are required. This is not available in a primary health care level but only available in Medical Colleges and Head Quarters hospitals.

Since leucocyturia had a significant association with ASB ($p<0.001$), this test can be used as a simple and cost effective screening test in a primary health care level. Positive cases can be sent to higher centres for urine culture and sensitivity.

Based on the availability and accessibility at rural level, an algorythm has been developed, to assess and manage asymptomatic bacteriuria in diabetic women.

Algorythm to detect and manage ASB in Type - 2 Diabetic Women



Strength of the study

Rigid criteria for case selection, meticulous efforts to collect urine samples for microbiological study and comparability of the observation with previous reports make the study strong. Based on the study one can confidently consider asymptomatic bacteriuria in diabetic women if she has leucocyturia.

Limitations

Hb A_{1c} was not estimated.

Details of sexual habits and sexual hygiene were not elicited.

Suggestions

Prospective studies on follow-up of cases to asymptomatic bacteriuria in the clinical course and complications of diabetes will help us to decide the effect of asymptomatic bacteriuria and its metabolites on diabetes in order to arrive valid conclusion regarding treatment of these cases.

CONCLUSION

- The prevalence of asymptomatic bacteriuria in type 2 diabetic women was 22.56% and comparable with published reports.
- Asymptomatic bacteriuria was independent of age and duration of diabetes.
- Asymptomatic bacteriuria was significantly more among diabetics with nephropathy.
- Simple bedside method to screen asymptomatic bacteriuria is leucocyturia and it has a positive predictability (72.7%) to detect bacterial isolates.
- Among asymptomatic bacteriuria, gram negative isolates were greater than gram positive ones.
- Isolates were resistant to most of the commonly used antimicrobials (Ciprofloxacin, Ofloxacin, Gentamicin and Cefotaxime) in clinical practice.
- An algorythmic approach to find out asymptomatic bacteriuria has been designed.

SUMMARY

Asymptomatic bacteriuria has been demonstrated in type 1 and type 2 diabetes mellitus, however the prevalence varied in different series. Paucity of prospective studies from India made to initiate one such work in this part of the country. The aims and objectives were to find out the prevalence of asymptomatic bacteriuria in type 2 diabetic women, to analyse the spectrum of organisms and its drug sensitivity pattern, to correlate asymptomatic bacteriuria with patient status and to design an algorythm to detect and manage asymptomatic bacteriuria in diabetic women.

A rigid criteria was adopted to select and assess asymptomatic bacteriuria among 164 type 2 diabetic individuals which was compared with 56 healthy individuals as control. The data were analysed statistically. The results of the study revealed that asymptomatic bacteriuria was present among 22.56% diabetic women. It was independent of the patients age and duration of disease. However it was significantly more among diabetics than control. The observation of this study was comparable with published reports.

Among the complications, patients with nephropathy were more susceptible for asymptomatic bacteriuria ($p<0.001$). Gram negative organisms were more common than gram positive ones. Among the laboratory investigations, leucocyturia was found to be significantly associated with asymptomatic bacteriuria and recommended as an early marker to pickup asymptomatic bacteriuria even at primary health care level.

ABBREVIATIONS

ADA	:	American Diabetes Association
ASB	:	Asymptomatic bacteriuria
BMI	:	Body mass index
CVS	:	Cardiovascular system
CNS	:	Central nervous system
cfu	:	Colony forming units
C/S	:	Culture and sensitivity
DM	:	Diabetes mellitus
GFR	:	Glomerular filtration rate
HbA_{1C}	:	Haemoglobin A_{1C}
hpf	:	High power field
n	:	Number
NT	:	Not tested
OGTT	:	Oral glucose tolerance test
PMNLs	:	Polymorphonuclear leucocytes
PVD	:	Peripheral vascular disease
SD	:	Standard deviation
UTI	:	Urinary tract infections
WHO	:	World Health Organisation

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PROFORMA

Name: Height: Cms

Age: Weight: Kgs

Date: BMI: Kg/M^2

Serial No.:
OP No.:

Study/Control Group:

Duration of DM: Yrs. BP: mmHg

Complications: **Micro:**1. Retinopathy 2.Neuropathy 3.Nephropathy

Macro:1.CVS 2. CNS 3. PVD

Past H/O UTI: Yes / No

Blood:

Plasma glucose	Fasting		
	PG		
Urea			
Creatinine			

Urine: **Treatment:**

Albumin :

Sugar :

Microscopy

Leucocytes/hpf:

Culture & Sensitivity

Organisms:

Drugs Resistant:

Drugs Sensitive: